1 INTRODUCTION

1.1 Squamous Cell Carcinoma of the Head and Neck

Head and neck tumors account for approximately 40,000 new cases and 12,000 deaths each year in the United States. Worldwide, head and neck tumors are the leading cause of cancer mortality. The majority (90%) of head and neck tumors are squamous cell carcinoma (SCC) (1).

Cancer of the oropharynx is the largest subgroup of head and neck tumors. The oropharynx includes the soft palate, tongue base, tonsillar fossa, tonsillar pillars, and a portion of the posterior pharyngeal wall. The overall survival rate for these tumors is 55% for Caucasian Americans and 34% for African Americans. Survival rates are impacted by the high proportion of patients who present with advanced (stage III and IV) disease (60%). Survival is inversely related to tumor size and regional lymph node involvement (1).

Wide local excision alone or curative radiation therapy is often the treatment of choice for patients with stage I and II cancers of the oropharynx (T1 [0-2cm] and T2 [2-4cm] tumors with negative nodes). Surgery results in five-year disease-free survival for this group of patients from 40% to 75%. Disease control through primary surgery comes at a cost. Surgical removal of a large part of the base of the tongue may result in prolonged difficulties with dysphagia, dysarthria, aspiration and disfigurement (1).

Prior work has suggested that the immune system plays a role in the natural history of head and neck tumors (2). Correlation's have been demonstrated between survival and several measures of systemic immunity (3-5). More recently, interest in the role of apoptosis in tumor growth and response to chemotherapy and radiation has developed (6). Most investigators accept the notion that apoptosis is a naturally occurring phenomenon in malignancy and that tumor regression may be due, in part, to enhanced apoptosis. Changes in immune cell infiltration or changes in the degree of apoptosis in a tumor may represent early measures of immune function directed against a patient's tumor (6,7). These early characteristics of a tumor may correlate with clinical benefit following immune-based therapy (8).

1.2 Allovectin-7®

Allovectin-7® contains a DNA plasmid encoding the HLA-B7 heavy chain (a MHC-class I protein), and β2 microglobulin. Allovectin-7® is complexed with a cationic lipid mixture (DMRIE/DOPE) that promotes the uptake of plasmid DNA by tumor cells. Allovectin-7® is administered by direct intratumoral injection. Given that many tumors have deficient MHC-class I expression, expression of HLA-B7 following treatment with Allovectin-7® can potentially trigger a cell-mediated immune response against transfected tumor. HLA-B7 was chosen because of its infrequent expression in the United States population and the additional possibility of developing an allogeneic immune response in HLA-B7 negative patients (9,10).

The safety of Allovectin-7® was evaluated in preclinical animal studies by intravenous injection in mice and Cynomolgous monkeys at a substantial multiple of the anticipated human intratumoral dose. Doses up to 140X the human dose of 100 μg of the DNA/lipid complex had no adverse effects in animals (11).

In initial human studies in patients with malignant melanoma, Dr. Nabel and colleagues at the University of Michigan demonstrated gene transfer and expression of HLA-B7 following

administration of Allovectin-7®. Adverse events were mild to moderate and consisted primarily of injection site pain and/or inflammation (9).

Subsequent studies in patients with melanoma have demonstrated a high rate of gene transfer and protein expression with Allovectin-7®. In 14 HLA-B7 negative patients evaluated, HLA-B7 DNA was demonstrated in 9/14 (64%) and HLA-B7 RNA was demonstrated in 4/14 (29%). HLA-B7 protein was demonstrated in 11/14 (79%). Anti-HLA-B7 serum antibodies were not detected in any patient (10).

Clinical benefit has been observed in prior studies for several patients with advanced head and neck cancer. Eleven patients were evaluated in a Phase I/II study of Allovectin-7® in persistent, unresectable squamous cell carcinoma of the head and neck conducted under an Investigator IND (BB-IND 6398) by Jack L. Gluckman, M.D. and Lyon Gleich, M.D. at the University of Cincinnati Medical Center. The study design included 4 intratumoral injections of 10 μg Allovectin-7®. Four of 9 patients (44%) demonstrated a partial response. In 2 of these patients the tumor regressed completely, however a biopsy demonstrated histologic evidence of squamous cell carcinoma. Three of these patients demonstrated long-term survival with 1 patient alive for greater than 24 months with no clinical evidence of disease. Interestingly, this patient demonstrated persistent histologic cancer suggesting an active role of his immune system in controlling residual tumor (12,13).

Based on prior phase I and II studies, VCL-1005-206 was initiated to test higher doses of Allovectin-7® in patients with recurrent or persistent head and neck cancer and to evaluate the hypothesis that Allovectin-7® improves the quality of life of treated patients. In this study, patients receive 4 intratumoral injections of 100 μg of Allovectin-7®. To date, 31 patients have been enrolled. No drug-related serious adverse events have been reported. One episode of moderate pain and one episode of hypotension, both likely related to the injection procedure, were reported (13).

1.3 Rationale for current study

Given the activity of Allovectin-7® in patients with recurrent or persistent head and neck cancer, it appears appropriate to evaluate this treatment in patients with earlier disease. Such patients are likely to have a healthier immune system and therefore more likely to respond to immune-based therapies such as Allovectin-7®. The setting of resectable disease also offers the opportunity to evaluate the resected tumor specimen for evidence of immune activation. Such information will prove useful in improving upon this treatment in the future.

2 OBJECTIVES

2.1 Primary Objective

- Estimate tumor response to Allovectin-7® prior to surgery

2.2 Secondary Objectives

- Assess immune response to Allovectin-7® as manifested by tumor necrosis, tumor apoptosis, and lymphocytic infiltration
- Evaluate the toxicity of Allovectin-7® in this setting
- Evaluate time to disease progression